Schering-Plough
Global Drug Information Services
P.O. Box 599
Kenilworth, NJ 07033

May 4, 2007

Schering-Plough

Roger Citron, R.Ph.
Montana Dept of Public Health
& Human Services
rcitron@mt.gov and pdl@mt.gov
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Dear Mr. Citron:

In response to your unsolicited request* for medical and scientific information on Avelox® (moxifloxacin hydrochloride) for the Montana Medicaid Drug Use Review Board/Formulary Committee Meeting to be held on May 23, 2007, we are providing you with a Clinical Summary for Avelox. Additionally, we are enclosing new references added to the clinical summary since the last submission in April 2006.

New data in this summary includes information on the 2007 Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults.

The following representative can be contacted to answer questions and provide additional information regarding the submission materials:

Russell Fotheringham
Regional Account Manager
Schering-Plough Corporation
17122 E Daybreak Ln
Spokane Valley, WA 99016
Office: (509) 922-8286
Cell: (509) 280-6453
Fax: (509)922-8286
E-mail: russell.fotheringham@spcorp.com

* This information is provided as a professional service in response to your unsolicited inquiry. It is intended to provide you with a fair, balanced, and objective review of the available scientific literature and/or data that you requested. This response is not intended to offer recommendations for use of this or any product inconsistent with approved product labeling. Please refer to the package insert for full prescribing information.

Please refer to the enclosed product information sheet for full prescribing information.

Sincerely,

Richard K. Kull MD

Richard K. Kull, M.D.
Sr. Director, Global Medical Information

2007-14802
Enclosure:
Avelox Product Information sheet
Anzueto et al.
Keating et al.
LaPlante et al.
Mandell et al.
Morganroth et al.
Giordano et al.
Malangoni et al.

EXECUTIVE SUMMARY

In response to your unsolicited request, we are providing this document, the purpose of which is to supply information on the usage of Avelox® (moxifloxacin hydrochloride) Tablets and Avelox® (moxifloxacin hydrochloride in sodium chloride injection) IV Injection to assist you in your formulary decision-making process.

- Avelox is a broad-spectrum fluoroquinolone that is FDA approved for the following indications:

Indications:	Caused by:
Acute bacterial sinusitis (ABS)	*Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis*
Acute bacterial exacerbation of chronic bronchitis (ABECB)	*Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae,* methicillin-susceptible *Staphylococcus aureus,* or *Moraxella catarrhalis*
Community-acquired pneumonia (CAP)	*Streptococcus pneumoniae* (including multi-drug resistant strains[a]), *Haemophilus influenzae, Moraxella catarrhalis,* methicillin-susceptible *Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae,* or *Chlamydia pneumoniae*
Uncomplicated skin and skin structure infections (uSSSI)	methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*
Complicated skin and skin structure infections (cSSSI)	methicillin-susceptible *Staphylcoccus aureus, Escherichia coli, Klebsiella pneumoniae* or *Enterobacter cloacae*
Complicated Intra-Abdominal Infections (cIAI) including polymicrobial infections such as abscess	*Escherichia coli, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, Enterococcus faecalis, Proteus mirabilis, Clostridium perfringens, Bacteroides thetaiotaomicron,* or *Peptostreptococcus* species

[a] MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as PRSP (Penicillin-resistant *S. pneumoniae*) and are strains resistant to two or more of the following antibiotics: penicillin (MIC $\geq$ 2 µg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

- The clinical efficacy of Avelox has been demonstrated in the treatment of infection due to gram-positive and gram-negative organisms, including multi-drug resistant strains of *Streptococcus pneumoniae* and atypical pathogens commonly identified in community acquired pneumonia patients.

- Avelox offers convenient once daily dosing in a single 400 mg strength that does not require dosage adjustment upon transitioning from an intravenous (IV) to an oral (PO) route of administration.

- No dosage adjustment is required for Avelox in patients with renal or hepatic (Child Pugh Classes A and B)* impairment.

* The pharmacokinetics of moxifloxacin in severe hepatic insufficiency (Child Pugh Class C) have not been studied.

- Avelox is widely distributed throughout the body, with tissue concentrations* often exceeding plasma concentrations. Clinical pharmacokinetic studies have shown that Avelox attains high concentrations in the target tissues quickly, such as the alveolar macrophages and epithelial lining fluid,[1] in the sinus tissues,[2] as well as in the inflammatory fluids.[3]

- Avelox maintains concentrations above MIC_{90}† values for common pathogens associated with respiratory tract infections.[1, 2]

- Studies have shown that Avelox has proven superior efficacy in the treatment of CAP compared to levofloxacin,[4] ABS compared to cefuroxime axetil[5, 6], and ABECB compared to amoxicillin and clarithromycin.[7]

- Resistance to β-lactams and macrolides is an increasing concern among common respiratory pathogens. Avelox is bacteriocidal and has a dual mechanism of action, attributed to inhibition of both bacterial DNA gyrase and topoisomerase IV.[8] Avelox has shown that *in vitro*† resistance develops slowly via multiple-step mutations and has a decreased susceptibility to bacterial efflux mechanisms due to Avelox's bulky side chain at the C-7 position. In an *in vitro*† study, Avelox showed a lower propensity to select resistant mutants of *S. pneumoniae* after repeated overnight exposures to suboptimal concentrations compared with Levaquin‡ and Floxin‡.[9]

- *In vitro*† resistance to Avelox in fluoroquinolone-susceptible strains of *Streptococcus pneumoniae* occurred at a slower rate compared to levofloxacin and gatifloxacin and at approximately the same rate as gemifloxacin in a study that assessed free AUC/MIC breakpoints† to determine the emergence of resistance and the rate at which it occurs.[10]

Community Acquired Pneumonia (CAP)

- Avelox has proven efficacy (clinical and bacteriological) in the treatment of CAP, in healthy patients, patients who require hospitalization, as well as elderly patients, with a safety profile similar to it's comparators in clinical trials.

- A respiratory fluoroquinolone, such as moxifloxacin, is strongly recommended by the 2007 IDSA/ATS joint committee for the treatment of outpatients with comorbidities, in non-ICU inpatients, and for use in combination with a β-lactam for the treatment of ICU inpatients. According to the guidelines, clinical failures have not been reported in treatment of drug resistant *S. pneumoniae* CAP with moxifloxacin or gemifloxacin, whereas clinical failures have been reported with ciprofloxacin and levofloxacin.[11]

- In a comparative clinical trial, there was no significant difference between Avelox and Levaquin‡ with respect to cardiac safety, the primary endpoint of the study.[12]

- In a prospective, randomized, comparative clinical trial conducted in elderly patients, clinical cure rate at test-of-cure visit (primary endpoint) was not significantly different between the Avelox and Levaquin‡ treated patients (92.9% vs 87.9%, 95% CI, -1.9 to 11.9; p=0.2). However, significantly

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* **Tissue/fluid penetration is regarded as essential to therapeutic efficacy, but penetration levels have not been correlated to specific therapeutic results.**

† **The clinical significance of *in vitro* data is unknown.**

‡ Levaquin® (levofloxacin) and Floxin® (ofloxacin) are registered trademarks of Ortho-McNeil, Inc.

more patients treated with Avelox had an assessment of clinical recovery (resolution or improvement) by day 3-5 than Levaquin* treated patients (97.9% vs 90.0%, 95% CI, 1.7-14.1; p=0.01).[4]

- Avelox has proven efficacy in treating patients with severe CAP. In patients who require initial IV therapy, a significantly faster IV to oral transition by day 5 was observed in patients receiving Avelox versus the comparator (73% vs 60%, respectively, p<0.01) (includes Augmentin†, Biaxin‡, Trovan§, Levaquin*).[13]

- In comparative clinical trials, Avelox was shown to be as effective as standard treatment with an advanced macrolide either alone or with a β-lactam[14-17] and more effective than an IV/PO regimen of Augmentin† with or without Biaxin‡.[18]

Acute Bacterial Sinusitis (ABS)

- In comparative clinical trials, Avelox has proven to be as effective as its comparators, including Ceftin†,[5, 19] Ketek**,[20] Trovan§,[21] and Augmentin†,[22] for the treatment of acute bacterial sinusistis, in a convenient, once daily dosing regimen.

- When compared to Levaquin*, a retrospective, claims database analysis study demonstrated that patients who were prescribed Avelox within 5 days of diagnosis for acute bacterial rhinosinusitis had a 30% to 35% lower probability of sinusitis recurrence (p=0.0005) and a significantly lower treatment failure rate (10.0% Avelox vs 13.9% Levaquin (p=0.0003).[6] Overall, 3358 episodes of ABS were treated with Avelox and 1522 episodes were treated with Levaquin.

- In a prospective, comparative clinical trial, a significantly greater number of patients treated with Avelox 400 mg for 10 days, reported feeling better by day 3 than the comparator (Augmentin† 875 mg twice daily) treated patients (24% vs 14%, respectively, p<0.02).[22]

- A prospective, non-comparative study was conducted in patients with acute maxillary sinusitis after first line treatment failure and acute sinusitis with high risk of complications where Avelox was administered for 7 days††. In this patient population, the reported clinical resolution rates were above 90%. In the per protocol population, improvement in condition was reported by 94.9% of patients on days 3-4 of treatment. Bacteriological success was seen in 97.2% of patients with maxillary sinusitis after first-line treatment failure and 95.2% of patients with sinusitis and risk of complications.[23]

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* Levaquin® (levofloxacin) and Floxin® (ofloxacin) are registered trademarks of Ortho-McNeil, Inc.
† Augmentin® (amoxicillin/clavulanic acid) and Ceftin® (cefuroxime axetil) are a registered trademark of GlaxoSmithKline.
‡ Biaxin® (clarithromycin) is a registered trademark of Abbott Laboratories.
§ Zithromax® (azithromycin) and Trovan® (trovafloxacin) are registered trademarks of Pfizer, Inc. Trovan is no longer marketed in the US.
** Ketek® (telithromycin) is a registered trademark of Sanofi-Aventis. Ketek is not indicated for the treatment of ABS.
†† For the treatment of acute bacterial sinusitis, the recommended dosing regimen of moxifloxacin is 400 mg for 10 days.

Acute Exacerbation of Chronic Bronchitis (AECB)

- Avelox® proved to be as effective as comparator treatment regimens (including amoxicillin, Biaxin* or Ceftin†) for the treatment of acute exacerbation of chronic bronchitis.[7]

- In the MOSAIC trial, Avelox treated patients showed a statistically significant lower mean time to the next acute exacerbation of acute bronchitis than the comparator treated patients (amoxicillin, Biaxin*, or Ceftin†) (p=0.03).[7]

- Avelox treated patients also had a signficantly lower frequency of additional antibiotic therapy in the per protocol and intent to treat populations (p=0.045 and p=0.006, respectively) and a higher proportion of Avelox treated patients received no concomitant steroid therapy or had no change in their existing steroid regimen (p=0.03 in the intent to treat population).[7]

- In a multi-center, observational study, the mean time to recovery was statistically significantly shorter in Avelox treated patients (4.6 ± 3.3 days) versus the comparator (5.8 ± 4.6 days) (p<0.01).[24]

Uncomplicated and Complicated Skin and Skin Structure Infections

- Avelox is indicated for treatement of uncomplicated skin and skin structure infections due to methicillin susceptible *Staphylococcus aureus* or *Streptococcus pyogenes* and has proven to be as effective, clinically and bacteriologically, as cephalexin, with a comparable safety profile.[25]

- Avelox received FDA approval (June, 2005) for the treatment of complicated skin and skin structure infections due to methicillin susceptible *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter cloaca*. Clinical studies have proven that IV/PO Avelox is as effective, clinically and bacteriologically, as Zosyn‡ or Augmentin† (IV§/PO).[26, 27]

Complicated Intra-abdominal Infections

- Avelox received FDA approval on November 22, 2005 for the treatment of complicated intra-abdominal infections including polymicrobial infections such as abscess caused by *Escherichia coli*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, *Enterococcus faecalis*, *Proteus mirabilis*, *Clostridium perfringens*, *Bacteroides thetaiotaomicron*, or *Peptostreptococcus* species.

- The safety and efficacy of Avelox have been demonstrated in the treatment of complicated intra-abdominal infections when compared to alternate treatment regimens. Two clinical studies have proven that IV/PO Avelox is as effective, as Zosyn‡ followed by Augmentin† and Rocephin®** plus IV metronidazole followed by Augmentin†, in patients with complicated intra-abdominal infections.[28, 29]

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* Biaxin® (clarithromycin) is a registered trademark of Abbott Laboratories.
† Augmentin® (amoxicillin/clavulanic acid) and Ceftin® (cefuroxime axetil) are a registered trademark of GlaxoSmithKline.
‡ Zosyn® (IV piperacillin/tazobactam) is a registered trademark of Wyeth Pharmaceuticals, Inc.
§ IV amoxicillin clavulanate is not FDA approved.
** Rocephin® (IV ceftriaxone) is a registered trademark of Roche Pharmaceuticals.

Safety

- Avelox is contraindicated in persons with a history of hypersensitivity to moxifloxacin or any member of the quinolone class of antimicrobial agents.

- Anaphylactic reactions, some following the first dose, have been reported in patients receiving quinolone therapy including moxifloxacin.

- The safety and effectiveness of Avelox in pediatric patients, adolescents (less than 18 years of age), pregnant women, and lactating women have not been established.

- Avelox has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class 1A or Class III antiarrhythmic agents, due to limited clinical experience. Avelox should be used with caution when given together with drugs that may prolong the QT interval and in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia.

- Two large, prospective, comparative clinical trials were conducted that evaluated the cardiac safety of Avelox to comparators (including alatrofloxacin/trovafloxacin and levofloxacin).[12, 18] In these studies, both moxifloxacin and comparator drugs were associated with a change in the QT interval. However, no cardiovascular morbidity and mortality were associated with the QT interval prolongation due to Avelox in these studies. Moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients. The drug should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents, due to the lack of clinical experience with the drug in these patient populations. (Please see the Avelox Product Information Sheet for complete Warnings, Precautions, and Adverse Events).

- As with all quinolones, Avelox should be used with caution in patients with known or suspected CNS disorders or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold.

- In large clinical trials, the most common adverse events occurring in $\geq$2% of patients were nausea (6%), diarrhea (5%), and dizziness (2%).

- A retrospective analysis study on the use of Avelox and its effect on glucose homeostasis found that the incidence of hypo- and hyper-glycemia was similar between Avelox and its comparators (broad spectrum penicillins (amoxicillin, Augmentin*, cephalosporins [Ceftin*]), macrolides (Zithromax†, Biaxin‡), doxycycline, and other fluoroquinolones (Trovan†, Levaquin§).[30]

- *Clostridium difficile* associated diarrhea, including pseudomembranous colitis, has been reported with nearly all antibacterial agents, and is a class warning.

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* Augmentin® (amoxicillin/clavulanic acid) and Ceftin® (cefuroxime axetil) are a registered trademark of GlaxoSmithKline.

† Zithromax® (azithromycin) and Trovan® (trovafloxacin) are registered trademarks of Pfizer, Inc. Trovan is no longer marketed in the US.

‡ Biaxin® (clarithromycin) is a registered trademark of Abbott Laboratories.

§ Levaquin® (levofloxacin) is a registered trademark of Ortho-McNeil, Inc.

Studies Published Since Previous Review

Citation: Anzueto A, Niederman MS, Pearle J, et al. Community-acquired pneumonia recovery in the elderly (CAPRIE): efficacy and safety of moxifloxacin therapy versus that of levofloxacin therapy. *Clin Infect Dis*. 2006;42(1):73-81. [4]

Location	Trial Design	Inclusion Criteria	Exclusion Criteria
47 centers in the US	Prospective, randomized controlled, double-blind, double-dummy, multi-center, comparative study conducted from November 2002 to April 2004	Hospitalized elderly patients (≥65 years), requiring initial IV therapy that also have radiologically-confirmed evidence of a new or progressive infiltrate consistent with pneumonia and ≥2 of the following: productive cough with purulent and/or mucopurulent sputum; or change in character of sputum; dyspnea or tachypnea; rigors or chills; pleuritic chest pain; auscultatory findings on pulmonary examination of rales/crackles and/or evidence of pulmonary consolidation; fever or hypothermia; and white blood cell count ≥10,000/mm^3, or ≥15% immature neutrophils (bands), regardless of the peripheral WBC count or leukopenia with a total WBC count <4500/mm^3.	Hospitalization for >48 hours prior to development of pneumonia; presence of end-organ damage or shock with need for vasopressors for >4 hours; need for mechanical ventilation; implanted cardiac defibrillator; significant brachycardia with heart rate <50 beats/min; systemic antibacterial therapy for >24 hours within 7 days of enrollment unless the patient was deemed to have therapy failure after receiving >72 hours of a non-fluoroquinolone antibiotic; mechanical endobronchial obstruction; known or suspected active tuberculosis or endemic fungal infection; neutropenia; chronic therapy (≥2 weeks) with known immunosuppressant therapy; known HIV infection with a CD4 count <200/mm^3; severe hepatic insufficiency; renal impairment (measured or calculated serum creatinine <20 ml/min); uncorrected hypokalemia; known prolongation of the QT_c interval or use of Class IA or Class III antiarrhythmics; previous history of tendinopathy with quinolones; or known hypersensitivity to study medications.

Sample Characteristics – No. of Patients

	Moxifloxacin	Levofloxacin	Total
Enrolled			401
ITT	195	199	394
PP	141	140	281

ITT = intent to treat (valid for safety)
PP = per protocol.

Treatment and Dosage Regimens

- **Moxifloxacin** 400 mg IV/PO QD
- **Levofloxacin** 500 mg IV/PO QD

Both treatment groups were treated for a total of 7-14 days

Patients with documented or calculated creatinine clearance of 20-49 ml/min in the levofloxacin groups were dose adjusted and received an IV levofloxacin 500 mg loading dose followed by 250 mg QD for the total therapy duration of 7-14 days.

Moxifloxacin treated patients with reduced creatinine clearance did not require dosage adjustment.

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response at test of cure (TOC) visit (5-21 days post- therapy)
- **Secondary** – Clinical response at the during therapy (day 3-5) visit and bacteriologic response at the TOC visit.
- **Health resource utilization assessment** – Collected at the TOC visit and included length of hospital stay, length of stay in an intensive care unit (ICU), total days of antimicrobial therapy, and duration of IV therapy.

Safety

Assessed by incidence rate of adverse events, lab data (including blood and urine samples for hematology, chemistry, coagulation, and urinalysis).

- Demographic and baseline medical characteristics were similar for both groups.
- Patients presenting with co-morbidities such as cardiac disorders (including coronary artery disease, congestive heart failure, ischemic disorders), respiratory disorders (including bronchospasm and obstruction, parenchymal lung disorders, conditions associated with abnormal gas exchange) and diabetes mellitus, however, there was no statistical significance in the incidence of any of these co-morbidities between treatment groups.

Efficacy Analysis in the PP Population

	Moxifloxacin (n=140)	Levofloxacin (n = 141)	95% CI (p-value)
Clinical cure at TOC	92.9%	87.9%	-1.9-11.9 (P=0.2)
Clinical cure for the microbiolog-valid population	81.0% (17/21)	76.7% (23/30)	-0.22-0.31 (P=0.98)
Bacteriologic success at TOC*	81.0% (17/21)	75.0% (21/28)	- (P=0.9)

*included patients with eradication and presumed eradication of causal pathogen

- Significantly more moxifloxacin treated patients in the clinically valid population recovered faster clinically (by day 3-5) (97.9%) than levofloxacin treated patients (90.0%) (95% CI, 1.7-14.1; p=0.01).
- Total hospital stay (±SD was 7.5 ± 4.2 days in the moxifloxacin arm and 7.5 ± 4.6 days in levofloxacin arm, p=0.95) and mean hospital stay after initiation of treatment (±SD was 6.8 ± 4.1 days in the moxifloxacin arm and 6.8 ± 4.6 days in levofloxacin arm, p=0.95) was not statistically significant between treatment groups
- Mean stay in the ICU was not statistically significant between treatment groups.

Summary of Adverse Events (ITT Population)

Adverse Events (Aes)	Moxifloxacin n =195	Levofloxacin n =199
Treatment emergent AEs	164 (84.1%)*	146 (73.4%)
Discontinuation due to AEs	15 (7.7%)	20 (10.1%)
Serious AE	46 (23.6%)	45 (22.6%)
Death	15 (7.7%)	11 (5.5%)
Drug-related AE (all)	51 (26.2%)	45 (22.6%)

*p=0.01

- None of the deaths were judged to be drug-related but related to the patient's comorbid diseases, as determined by the investigators.

Adverse Event	Moxifloxacin (n = 195)	Levofloxacin (n = 199)
Diarrhea	11 (5.6%)	10 (5.0%)
Oral candidiasis	7 (3.6%)	7 (3.5%)
Nausea	3 (1.5%)	4 (2.0%)
Clostridium difficile infection/colitis	1 (0.5%)	6 (3.0%)
Cardiac events	2 (1.0%)	7 (3.5%)
Atrial fibrillation	0	3 (1.5%)
Ventricular tachycardia	1 (0.5%)	1 (0.5%)
Acute myocardial infarction	0	1 (0.5%)
Atrial flutter	0	1 (0.5%)
Congestive heart failure	0	1 (0.5%)
Cardio-respiratory arrest	0	1 (0.5%)
Supraventricular tachycardia	1 (0.5%)	0
Torsades de pointes	0	1 (0.5%)
Chest pain	0	1 (0.5%)
Heart rate increased	0	1 (0.5%)

- There was no clinically significant difference between treatment groups for laboratory tests or vital signs assessed.

Citation: Keating, KN, Friedman, HS, Perfetto, EM. Moxifloxacin versus levofloxacin for treatment of acute rhinosinusitis: a retrospective database analysis of treatment duration, outcomes, and charges. *Current Medical Research and Opinion.* 2006;22(2):327-333.[6]

Location	Trial Design	Study methods
The study was performed using data from the PharMetrics' database which contains demographic information and medical and pharmaceutical claims for more than 55 million patients that cover over 2 billion healthcare transactions, including prescriptions, office visits, hospital stays, and diagnostic tests from at least 75 different health plans. The database includes both inpatient and outpatient diagnoses and procedures, both retail pharmacy and mail order prescription records, as well as data on Medicare Risk patients.	A retrospective, claims database study conducted between April 2000 and March 2002.	Treatment episodes were selected from the database by first identifying all office or hospital outpatient visits with an ICD-9 diagnosis of acute rhinosinusitis (AS). For each visit, the date of the diagnosis of acute rhinosinusitis was determined to be the episode index date. The database was then searched for all episodes in which moxifloxacin or levofloxacin were prescribed within five days from the episode index date. The date of the prescription for either moxifloxacin or levofloxacin was defined as the drug index date. The treatment episodes were monitored for a 30 day period following the drug index date, or in the case of treatment failure, for 30 days after the second antibiotic prescription was filled and continued until no treatment failure was observed.

Sample Characteristics – No. of Acute Sinusitis Episodes	Treatment	Criteria for Evaluation
Moxifloxacin 3,358 **Levofloxacin** 1,522 • The sample size above reflects the number of AS episodes in which the listed product was the initial treatment. • Baseline characteristics were similar between the two groups with the exception of a few differences which were significant. o Moxifloxacin treated patients had fewer patients with a compromised immune history (24.8% moxifloxacin, 28.7% levofloxacin, p = 0.003) and fewer episodes beginning in an emergency department (0.1% moxifloxacin, 0.5% levofloxacin, p = 0.008). • Log-lagged charges (the sum of the charges from all facility, professional service, and outpatient claims that occurred in the 180-day period prior to the beginning of the treatment episode) were lower in the moxifloxacin group at baseline (6.17 moxifloxacin, 6.39 levofloxacin, p = 0.008).	AS episodes were included in the study analysis, only where either moxifloxacin or levofloxacin were identified as the initial therapy.	• Endpoints measured in this study included total therapy duration and monotherapy duration, treatment failure, recurrence of infection, and treatment costs.

Ordinary Least Squares Regression Results*

	Duration of original prescription (days supplied)	Monotherapy duration (days supplied)	Duration of all antibiotics (days supplied)	Treatment Charges ($)	Log of treatment charges ($)
Treatment (moxifloxacin=1) *Estimate (p-value)*	-1.65 *(<0.0001)*	-2.06 *(<0.0001)*	-1.97 *(<0.0001)*	-37.94 *(0.0055)*	-0.093 *(<0.0001)*
F statistic	26.59 *(<0.0001)*	26.75 *(<0.0001)*	22.67 *(<0.0001)*	5.12 *(<0.0001)*	23.26 *(<0.0001)*
R^2	0.047	0.049	0.040	0.009	0.041

* All regression models controlled for: diabetes, compromised immune history, log lagged charges, start of episode in the emergency department, acute steroid use, gender, Charlson-Deyo comorbidity score, and age.

- The average duration of therapy was 10.4 days in the moxifloxacin group versus 12.4 days in the levofloxacin group ($p < 0.001$).
- Moxifloxacin treated patients had a 30-35% lower probability of recurrence than levofloxacin treated patients ($p=0.0005$).
- The observed failure rate was also significantly lower in the moxifloxacin group compared to the levofloxacin group (10.0% versus 13.9%, respectively, $p = 0.0003$).
- Cost analysis also demonstrated that the average total treatment charges ($171 moxifloxacin verses $212 levofloxacin, $p = 0.03$) and average pharmacy charges ($103 moxifloxacin versus $117 levofloxacin, $p < 0.0001$) were significantly lower in the moxifloxacin-initiated group (costs were adjusted to 2002 dollars using the Consumer Price Index).
- Ordinary least squares analysis demonstrated that the duration of the original prescription was 1.65 days shorter for the moxifloxacin group compared to the levofloxacin group.
- The duration of therapy, both monotherapy and duration of all antibiotics, was significantly shorter in the moxifloxacin treated group when compared to the levofloxacin group (2.06 and 1.97 days, respectively, $p<0.0001$).

Citation: Morganroth J, Di Marco J, Anzueto A, et al. A Randomized Trial Comparing the Cardiac Rhythm Safety of Moxifloxacin vs Levofloxacin in Elderly Patients Hospitalized with Community Acquired Pneumonia. *Chest.* 2005;128:3398-3406.[12]

Location	Start Date and Duration	Trial design	Inclusion Criteria
47 hospitals in the United States.	November 2002 – April 2004	Prospective, randomized, double-blind trial	≥65 years old with clinical signs and symptoms of CAP who required initial parenteral therapy with radiologically confirmed evidence of a new or progressive infiltrate(s) consistent with bacterial pneumonia and at least two of the following findings: productive cough with purulent or mucopurulent sputum/tracheobronchial secretions (≥25 polymorphonuclear neutrophils/low-power field on Gram stain) or change in the character of sputum (increased volume or purulence); dyspnea or tachypnea (respiratory rate >20 breaths/min); rigors or chills; pleuritic chest pain; auscultatory findings on pulmonary examination of rales/crackles and/or evidence of pulmonary consolidation; fever (oral temperature ≥38°C/100.4°F, rectal temperature ≥39°C/102.2°F, or tympanic membrane temperature ≥38.5°C/101.2°F) or hypothermia (rectal or core temperature <35°C/95.2°F); and WBC count ≥10,000/μL or ≥ 15% immature neutrophils (bands), regardless of the peripheral WBC count, or leukopenia with a total WBC count <4,500/μL.

Sample Characteristics*

Characteristics	Moxifloxacin n=195 (%)	Levofloxacin n=199 (%)
Male	100 (51.3)	102 (51)
Race		
White	166 (85.1)	170 (85.4)
Black	15 (7.7)	13 (6.5)
Hispanic	14 (7.2)	14 (7.0
Asian	0	2 (1.0)
Mean age ± SD (range), yr	78.1 ± 7.5 (54-95)	77.5 ± 7.7 (55-98)
ATS severity, severe	33 (16.9)	37 (18.6)
PSI score		
missing	30 (15.4)	37 (18.6)
1	3 (1.5)	0
2	29 (14.9)	25 (12.6)
3	54 (27.7)	25 (12.6)
4	65 (33.3)	74 (37.2)
5	14 (7.2	12 (6.0)
Comorbidities		
Cardiac disorder	140 (74.8)	152 (76.4)
Diabetes mellitus	52 (26.7)	63 (31.7)

*All p values for treatment differences were nonsignificant

Treatment and Dosage Regimens

Patients randomized to receive either:

A. IV Moxifloxacin
400 mg QD then
PO 400 mg QD after ≥ 2 days*

B. IV Levofloxacin
500 mg QD then
PO 500 mg QD after ≥ 2 days*

Both groups continued treatment for 7 – 14 days and were followed for 5 – 21 days after therapy

The dose of levofloxacin was adjusted for patients with creatinine clearance values from 20 to 50 mL/min based on approved product labeling, *ie*, a 500-mg loading dose followed by 250 mg qd. Patients randomized to moxifloxacin did not require dose adjustments in the presence of renal insufficiency.

*Switch to PO if *a priori* criteria were met, ie:
improved on IV therapy
afebrile for ≥ 8 h
able to tolerate oral food, fluids, medications without vomiting or diarrhea.

Criteria for Evaluation

Safety

- **Primary*** – Primary composite score derived from 72h Holter monitor recording of the following:

1). cardiac arrest fatal and non-fatal including ventricular fibrillation and asystole
2). sustained monomorphic or polymorphic VT without cardiac arrest (>30s).
3). nonsustained monomorphic VT (≥10 beats, <30s), including *torsade de pointes* (≥10 beats of changing morphology during the run with a long QTc interval).

- **Secondary** – A secondary composite score including:

1). any occurrence of atrial fibrillation (>120 beats/min) with rapid ventricular response; new-onset atrial fibrillation; any nonsustained supraventricular tachycardia (SVT) with a rate >120 beats/min; new-onset sustained (> 60 s) SVT; third degree atrioventricular block; long RR pauses (> 3 s in patients with sinus rhythm and >5 s in patients with atrial fibrillation), and overall mortality.

*The primary safety variable was to be coded as 1 if the patient experienced any of the events described above or 0 if otherwise.

Results: **Primary and Secondary Cardiac Rhythm Safety End Points in Patients in the Safety Population Who Had Holter Data***

End Points	Moxifloxacin (n = 192)	Levofloxacin (n = 195)	95% CI
Primary composite			
Sustained VT (>30 s)	1 (0.5)	0	- 3.2 to 7.5
Nonsustained VT (≥10 beats, ≤30 s)	14 (7.3)	10 (5.1)	-3.0 to 7.3
Uniform morphology	13 (6.8)	9 (4.6)	-1.0 to 2.1
Multiple polymorphic VT morphologies	1 (0.5)	0	-2.0 to 1.0
Torsade de pointes	0	1 (0.5)	-1.0 to 2.1
Cardiac arrest	1 (0.5)†	0	-1.0 to 2.1
Total patients	16 (8.3)	10 (5.1)	-1.8 to 8.2
Secondary composite			
Atrial fibrillation (>120 beats/min)	20 (10.4)	22 (11.3)	-7.6 to 5.8
New-onset atrial fibrillation	10 (5.2)	9 (4.6)	-4.2 to 5.4
Nonsustained SVT (>120 beats/min)	125 (65.1)	125 (64.1)	-9.0 to 11.0
New-onset SVT (> 60 s)	6 (3.1)	4 (2.1)	- 2.6 to 4.8
Third-degree atrioventricular block	2	0	-0.9 to 3.0
Long RR pauses (>3 s)	0	0	-0.5 to 0.5
Total patients	141 (73.4)	140 (71.8)	-7.8 to 11.0
Other Holter findings			
Nonsustained VT (>3, <10 beats)	69 (35.9)	69 (35.4)	-9.5 to 10.6
Ventricular premature beats	183 (95.3)	188 (96.4)	-5.6 to 3.4

*Data are expressed as the No. of patients (%) who experienced an event of that type. Each event is counted only once per patient. One moxifloxacin-treated patient had both VT >30 s and VT ≥10 beats. All p values for treatment differences were nonsignificant (>0.05).

†Resulting from respiratory failure following do-not-resuscitate order.

- Sixteen moxifloxacin-treated patients (8.3%) and 10 levofloxacin-treated patients (5.1%) had a primary composit cardiac event (p=0.29)
- Most events were nonsustained ventricular tachycardia (14 patients receiving moxifloxacin, 7.3%; and 10 patients receiving levofloxacin, 5.1%)
- One moxifloxacin-treated patient sustained monomorphic VT (>30 s), and one levofloxacin-treated patient had *torsade de pointes.*
- Mean ± SD QTc (Fridericia formula) change on day 3 was +6.4 ± 23.2 ms for moxifloxacin and -2.5 ± 22.9 ms for levofloxacin (p=0.04)
- No deaths clearly related to study drugs occurred during the observation period.

Citation: Giordano P, Song J, Pertel P, Herrington J, Kowalsky S. Sequential intravenous/oral moxifloxacin versus intravenous piperacillin-tazobactam followed by oral amoxicillin-clavulanate for the treatment of complicated skin and skin structure infection. *Int J Antimicrob Agents.* Nov, 2005;26(5):357-365.[27]

Location	Start Date and Duration	Trial design	Inclusion Criteria
59 centers in 6 countries (United States, Canada, Israel, Chile, Argentina, and Peru)	December 12, 2000 to July 20, 2003	Prospective, randomized, double dummy, double-blind, multi-center	Male and female patients aged 18 years or older who were hospitalized with a diagnosis of complicated skin and skin structure infections requiring a minimum of one week of antimicrobial therapy.

Sample Characteristics – No. of Patients	Moxi	Comp	Total
Randomized	NR	NR	617
ITT population	298	303	601
PP population	180	187	367
Valid for Microbiology	119	119	238

ITT = intent to treat (valid for safety); PP = per protocol (valid for efficacy).

NR = Not reported

Treatment and Dosage Regimens

- **Rx1:** IV/PO moxifloxacin 400 mg QD
- **Rx2:** IV piperacillin/ tazobactam 3.0 g/ 0.375 g Q6H followed by PO amoxicillin/ clavulanic acid suspension 800 mg Q12H

IV treatment was administered for a minimum of 3 days and combined IV/PO treatment duration was 7 to 14 days.

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response at test of cure (TOC), 10-42 days after the last dose of study drug in the efficacy-valid population.
- **Secondary** – Bacteriological response at the TOC in the microbiologically-valid population. Clinical response on the day of IV to PO switch or on treatment day 3-5, and at the end of therapy in the efficacy-valid population and all time points (including TOC) for the intent-to-treat and microbiologically-valid population.

Safety

Monitoring for adverse events, physical examination, ECG, and laboratory tests including hematology, chemistry, and urinalysis.

- The type of complicated skin and skin structure infections treated in this trial included infected ischemic ulcer or decubitus ulcer, diabetic foot infections, abscesses, carbuncles, infections requiring surgical intervention and antimicrobial therapy, deep soft tissue infections (including infections from surgical wound), and bite wound infections from human or animal.

Response at the Test of Cure for Subjects Valid for Efficacy

	Avelox	Piperacillin/tazobactam amoxicillin/clavulanic acid	95% Confidence Interval
Clinical Cure Rate	143/180 (79%)	153/187 (82%)	(-12.4% 3.29%)
Bacteriological Eradication[a]	92/119 (77%)	96/119 (81%)	(-14.8%, 5.2%)

[a] Includes confirmed eradication and presumed eradication

Clinical Response by Infection Type at the Test of Cure for Subjects Valid for Efficacy

	Avelox (n=180)	Comparator (n=187)
Abscess	42/53 (79%)	52/56 (93%)
Cellulitis ♠	36/43 (84%)	38/43 (88%)
Diabetic foot infection♦	25/37 (68%)	25/41 (61%)
Infected ischemic ulcer or decubitus ulcer	10/13 (77%)	6/10 (60%)
Surgical wound infection	11/12 (92%)	8/8 (100%)
Complicated erysipelas	-	2/2 (100%)
Infection with traumatic lesion♣	11/12 (92%)	10/13 (77%)
Other infection types•	8/10 (80%)	12/14 (86%)

♠ Cellulitis includes cellulitis, cellulitis with lymphedema, cellulitis with venous stasis

♦ Avelox is not indicated for the treatment of diabetic foot infection

♣ Infection with traumatic lesion includes infection of traumatic lesion, bite wound infection, and infection with trauma

• Other includes infection hematoma, carbuncles, septic bursitis, other infected ulcers, infected wound, phlegmon, peri-rectal skin infection, infection of deep soft tissue and lymphangitis

- Polymicrobial infections were identified in 50% of Avelox patients and 45% of comparator patients and were more common in patients diagnosed with abscesses, diabetic foot infections, cellulitis, and surgical wound infections. For all infection types, *Staphylococcus aureus* was the most frequently isolated organism.

Table 3: Clinical Cure and Bacteriological Eradication Rates at the Test of Cure by Subject by Organism for Subjects Valid for Efficacy with Selected Causative Pretherapy Skin Organisms

Organism	Avelox n/N (%)		Comparator n/N (%)	
	Clinical Cure	Bacteriological Eradication[a]	Clinical Cure	Bacteriological Eradication[a]
Gram-positive aerobes				
Staphylococcus aureus	50/64 (78%)	50/64 (78%)	47/59 (80%)	47/59 (80%)
Oxacillin-susceptible (MSSA)	44/54 (81%)	44/54 (81%)	42/52 (81%)	42/52 (81%)
Oxacillin-resistant (MRSA)	6/10 (60%)	6/10 (60%)	5/7 (71%)	5/7 (71%)
Streptococcus pyogenes	13/18 (72%)	13/18 (72%)	8/12 (67%)	8/12 (67%)
Streptococcus agalactiae	7/13 (54%)	7/13 (54%)	19/25 (76%)	20/25 (80%)
Streptococcus dysgalactiae	5/6 (83%)	5/6 (83%)	5/7 (71%)	5/7 (71%)
Enterococcus faecalis	12/18 (67%)	12/18 (67%)	9/12 (75%)	9/12 (75%)
Gram-negative aerobes				
Enterobacteriaceae				
Escherichia coli	7/8 (88%)	7/8 (88%)	11/12 (92%)	11/12 (92%)
Klebsiella pneumoniae	5/6 (83%)	5/6 (83%)	4/7 (57%)	4/7 (57%)
Proteus mirabilis	3/5 (60%)	3/5 (60%)	5/6 (83%)	5/6 (83%)
Enterobacter cloacae	4/5 (80%)	4/5 (80%)	1/2 (50%)	1/2 (50%)
Non-Enterobacteriaceae				
Pseudomonas aeruginosa	4/5 (80%)	4/5 (80%)	7/11 (64%)	6/11 (55%)
Acinetobacter spp.[b]	3/5 (60%)	3/5 (60%)	5/6 (83%)	5/6 (83%)
Gram-positive anaerobes				
Peptostreptococcus spp.[c]	6/10 (60%)	6/10 (60%)	11/12 (92%)	11/12 (92%)
Gram-negative anaerobes				
Bacteroides spp.[d]	9/9 (100%)	9/9 (100%)	9/10 (90%)	9/10 (90%)
Prevotella spp.[e]	9/14 (64%)	9/14 (64%)	9/11 (82%)	9/11 (82%)
Monomicrobial	50/59 (85%)	50/59 (85%)	55/65 (85%)	55/65 (85%)
Polymicrobial	42/60 (70%)	42/60 (70%)	41/53 (77%)	41/53 (77%)

[a] Includes eradication and presumed eradication

[b] *Acinetobacter* spp. includes *Acinetobacter* sp. and *Acinetobacter lwoffi*

[c] *Peptostreptococcus* spp. includes *Peptostreptococcus* sp, *Peptostreptococcus anaerobius, Peptostreptococcus asaccharolyticus, Peptostreptococcus magnus, Peptostreptococcus prevotii, Peptostreptococcus tetradius*, and *Peptostreptococcus micros*

[d] *Bacteroides* spp includes *Bacteroides* sp, *Bacteroides fragilis, Bacteroides merdae, Bacteroides stercoris, Bacteroides thetaiotaomicron*, and *Bacteroides uniformis*

[e] *Prevotella* spp. includes *Prevotella* sp., *Prevotella buccae, Prevotella oris, Prevotella bivia, Prevotella disiens, Prevotella melaninogenica, Prevotella oralis, Prevotella intermedia, Prevotella tannerae*, and *Prevotella veroralis*

n = number of clinical cures or bacteriological eradication

N = number of subjects with specified organism

MRSA = methicillin-resistant Staphylococcus aureus

MSSA = methicillin-susceptible Staphylococcus aureus

- Adverse event rates were comparable between the two treatment groups who received at least one dose of the study drug (ITT). Drug related adverse event was reported in 31% in the moxifloxacin treated patients and 30% in the comparator treated patients. In general, majority of AEs were mild or moderate intensity. Discontinuation rates due to AEs were similar in both treatment groups (9% Avelox, 10% comparator). In total, six deaths occurred during the study surveillance period (3 in each group). None of the deaths was related to study drugs. In treatment groups, diarrhea and nausea were the most common drug related AEs.

Citation: Malangoni MA, Song J, Herrington J, Choudhri S, Pertel P. Randomized contolled trial of moxifloxacin compared with piperacillin-tazobactam and amoxicillin-clavulanate for the treatment of complicated intra-abdominal infections. *Annals of Surgery.* August, 2006;244(2):204-211.[28]

Location	Start Date and Duration	Trial design	Inclusion Criteria
71 centers in 3 countries (United States, Canada, and Israel)	October 23, 2000 to April 22, 2003	Prospective, randomized, double-blind, comparative, multi-center clinical trial	Hospitalized male or nonpregnant female patients aged 18 years or older with suspected complicated intra-abdominal infection (intra-abdominal infection for which an operative procedure or percutaneous drainage was required for diagnosis and management) requiring treatment for at least 5 days. In this study, patients with the following cIAI were treated: intra-abdominal abscess, secondary bacterial peritonitis, appendicitis with evidence of perforation or abscess (duration of symptoms >24 hours), acute perforations of the stomach or duodenum if not operated on within 24 hours of perforation, traumatic perforation of the small bowel (excluding the duodenum) or large bowel if not operated on within 12 hours of perforation, perforation of the small bowel (excluding duodenum) or large bowel unrelated to trauma, and intra-abdominal infections related to previous intra-abdominal surgery.

Sample Characteristics – No. of Patients			
	Moxifloxacin	Comparator	Total
Enrolled	339	342	681
Valid for safety	329	327	656
Valid for efficacy	183	196	379
Valid for bacteriologic response	150	165	315

Treatment and Dosage Regimens

- **Rx1:** IV/PO moxifloxacin 400 mg QD*
- **Rx2**: IV piperacillin/tazobactam 3.0/0.375g Q6H followed by PO amoxicillin/ clavulanic acid 800 mg/114 mg Q12H*

* Duration of treatment was a minimum of 5 days and maximum 14 days. The transition from IV to PO treatment was determined by the investigator based on the patient's clinical status and ability to tolerate oral therapy.

Criteria for Evaluation

Efficacy

- **Primary** – Clinical response at day 25 to 50 days after study entry (test-of-cure, TOC) in the efficacy-valid population
- **Secondary** – Bacteriologic response at TOC in the bacteriologic response population

Safety

Based on vital signs, laboratory tests (standard serial renal, hepatic, and hematologic), ECG, adverse events, and deaths.

Clinical Response Rates(at TOC visit 25-50 days after study entry)

	Moxifloxacin n/N (%)	Comparator n/N (%)
Valid for efficacy		
Clinical Cure	146/183 (80%)	153/196 (78%)
Valid for bacteriologic eradication*		
Bacteriologic Eradication/ Presumed eradication	117/150(78%)	126/163 (77%)

*Subjects had documented pre-therapy intra-abdominal pathogens. Two subjects in the comparator arm had blood isolates only.

Clinical Response at the TOC Visit by Anatomic Site of Infection for Subjects Valid for Efficacy

Anatomic Site of Infection	Moxifloxacin n /N (%)	Comparator n/N (%)
Upper gastrointestinal tract (total)	**13/16 (81)**	**15/19 (79)**
Perforated stomach or duodenum	7/8 (87)	8/10 (80)
Other	6/8 (75)	7/9 (78)
Lower gastrointestinal tract (total)	**118/150 (79)**	**121/153 (79)**
Complicated appendicitis	84/113 (74)	91/115 (79)
Perforation small or large bowel	25/27 (93)	19/26 (73)
Ileocolic abscess	9/10 (90)	11/12 (92)
Post-operative upper gastrointestinal tract	**8/9 (89)**	**5/7 (71)**
Post-operative lower gastrointestinal tract	**7/8 (87)**	**12/17 (71)**

Bacteriologic Response at Test-of-Cure Visit for Microbiologically Valid Patients

Organism	Bacteriologic Eradication n/N (%)			
	Hospital-Acquired Infection		Community-Acquired Infection	
	Moxifloxacin	Comparator	Moxifloxacin	Comparator
Gram-Positive aerobes				
S. anginosus	7/8 (87)	4/4 (100)	18/26 (69)	35/44 (80)
S. constellatus	-	-	17/27 (63)	8/13 (62)
E. faecalis	4/4 (100)	2/6 (33)	4/7 (57)	6/9 (67)
E. avium	-	-	13/14 (93)	6/9 (67)
Gram-negative aerobes				
E. coli	9/9 (100)	6/10 (60)	57/78 (73)	63/80 (79)
K. pneumoniae	-	-	8/14 (57)	12/17 (71)
P.aeruginosa	-	-	17/22 (77)	13/18 (72)
Gram-negative anaerobes				
B. fragilis	5/6 (83)	4/9 (44)	30/35 (86)	32 41 (78)
B. thetaiotaomicron	2/2 (100)	6/9 (67)	27/34 (79)	21/29 (72)
B. uniformis	-	-	10/12 (83)	8/11 (73)
Total	**20/24 (83)**	**16/29 (55)**	**97/126 (77)**	**110/134 (82)**

- indicates fewer than 10 isolates in that setting

Overview of Safety Events and Survival

Event	Moxifloxacin N = 329 n (%)	Comparator N = 327 n (%)
Any adverse event	276 (84)	271 (83)
Any drug-related adverse event	82 (25)	90 (28)
Any serious adverse event	63 (19)	66 (20)
Discontinuation due to adverse event	34 (10.3)	28 (8.6)
Deaths	6	7

- The incidence of drug-related adverse events were similar between treatment groups.
- The most commonly reported adverse events were nausea, hypokalemia, abdominal pain, and constipation.
- Of the serious adverse events reported, 11 serious events in 10 moxifloxacin-treated patients and 7 serious events in 7 comparator-treated patients were judged to be possibly or probably drug-related.
- None of the deaths reported in the moxifloxacin and comparator-treated patients were judged by the investigators to be related to the study drug.

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